IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

David M. Anderson — Confirmation No. 7327

Serial No. 09/994,937 — Group Art Unit 1616

Filed November 28, 2001 — Examiner Webman

For SOLVENT SYSTEMS FOR PHARMACEUTICAL AGENTS

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF RICHARD TEMPLER
UNDER 37 C.F.R. §1.132

REMARKS

Richard Templer declares as follows:

1. I am a Professor and Head of the Department of Chemistry, and hold the Hofman Chair in Chemistry at Imperial College, London, the address of which is Exhibition Road, London SW7 2AZ, with telephone 011- 0207 594 5787. My vitae, including a list of publications, are attached as Appendix A.

2. My education and training have been as follows: in 1978 I undertook an undergraduate degree in Physics at the University of Bristol in the UK, then in 1981 did my doctoral studies at the University of Oxford, where I also undertook a two year research assistantship which completed in 1986. Following this I obtained a Harkness Fellowship and a Princeton Fellowship which I took to the Department of Physics in Princeton University, where I later became a Lecturer. I returned to the UK in 1989 on a Royal Society 1983 Fellowship which I held for two years at the University of Southampton before making my final move to the Department of Chemistry at Imperial College London, where I have been ever since. Over the past 20 years, my research, teaching and publishing have focused on, among other subjects, lyotropic phase behavior, kinetics of lyotropic phase behavior, phase behavior and energetics of lipid-water systems, lipid protein interactions, and drug membrane interactions, and my work has included, among other things, the preparation and use of phase diagrams, and the creation and experimental identification of the lyotropic liquid and liquid crystalline phases, including reversed cubic and reversed hexagonal phases, in lipid-water systems.

3. I do not hold a position with Lyotropic Therapeutics, Inc., which I understand to be the owner of the above-identified application.

4. My background and experience set forth in items 1 and 2 above, and my list of publications in refereed journals, establish my expertise in the field and qualify me to provide evidcnce on the level of skill of one of ordinary skill in the art to which the above-identified application pertains and to provide evidence on whether or not the application, as originally filed provides a complete written description of the invention which would enable one of ordinary skill in the art to make and use the invention described in the application.

5. I have read and understand U.S. Application Serial Number 09/994,934, Solvent Systems for Pharmaceutical Agents (the "Application").

6. It is my opinion that the Application provides a complete written description of the invention that would enable one of ordinary skill in the art to make and use the invention.

7. It is my opinion that the conclusions that the "predictability in the art is low", that "the quantity of experimentation need to make the invention is undue", and that "percent ranges of the claimed ingredients" are needed by those of skill in the art to make a "structured fluid", as set forth in the office action of January 10, 2007, are simply incorrect. Quite the contrary, the application as originally filed provides more than enough information to one of ordinary skill in the art to begin making and using structured fluids in the manner described almost immediately. That is, the compositions and solvent systems claimed in the application, particularly in the amendment filed December 15, 2006, could be produced by one of ordinary skill in the art without undue experimentation. Further, it is my opinion that the declaration of David Anderson dated December 15, 2006, whom I understand to be the inventor of the above-identified patent application, does not in any way conflict with my opinion. Rather, my opinion supports the conclusions drawn in the previously filed declaration of David Anderson.

8. At the outset, it should be understood that one of ordinary skill in the art pertaining to the claimed invention will have significant educational experience. I agree with David Anderson's declaration at item 4, that one of ordinary skill in the art will typically have the degree of Ph.D. in Chemical Engineering, Chemistry, Biochemistry or a related field. He or she will have engaged in research for 5-10 years and will have authored a few articles in refereed journals. There are scores of articles and textbooks available in the literature, taught in graduate courses, which are routinely referred to by practitioners of the art of colloidal systems, and in particular lyotropic liquid and liquid crystals. David Anderson's declaration dated December 15, 2007, references a number of exemplary documents in Attachment 3 and item 5. One of ordinary skill in the art would have access to those documents and others like those, including the references in the application itself, and would be well versed in identifying such documents. He or she would be well versed in the preparation and identification of various lyotropic liquid and liquid crystalline phases, including reversed cubic and reversed hexagonal phases, through the use of phase diagrams and understanding fundamental thermodynamic principles.

9. On review of the application, one of ordinary skill in the art would recognize that an important aspect is the identification of certain specified co-solvents that may be used to solubilize difficult to solubilize compounds (pharmaceutical actives) so that they incorporate into reversed cubic or reversed hexagonal phase materials when they otherwise would not do so or do so ineffectively (Page 4), and the patent application seeks to cover compositions so created by those co-solvents. One of ordinary skill in the art would recognize that such compositions also provide a solubilizing matrix into which the pharmaceutically active compound partitions preferentially over water or body fluid. (Page 38). Claim 1, for example, requires a composition of either or both reversed cubic or reversed hexagonal phase material comprising certain ingredients, namely, a polar solvent and lipid or surfactant, a difficult to solubilize compound, and one or more identified co-solvents, namely an essential oil or a specified dissolution / co-solubilization agents.

10. One of ordinary skill in the art, having the technical background, experience and skills described above, having reviewed the above-identified patent application would recognize that it set out a sequence of formulation rules in which each component class had a separable and controllable function which when correctly adjusted will solubilize difficult to solubilize compounds in an reversed hexagonal or reversed cubic phase. They would be able to practice the invention in the following way (this being understood to not be an exhaustive listing of all possible routes of using the invention described in the application).

A. He or she would start by selecting a compound of interest. He or she would be able to determine by reference to published literature or by simple, straight forward experimentation in the lab whether a compound was less than 5% soluble in soy bean oil (claim 1 et seq.).

B. He or she would select a polar solvent / lipid or surfactant system from those generally known in the art to potentially form reverse cubic phase or reverse hexagonal phase materials. This information would be readily ascertained from the type of literature one of ordinary skill in the art would have access to as is discussed above. Further, he or she may well select the PC / water system, which is both nearly universal in the art and used in one or more of the examples of the Application.

C. He or she would assemble a short list of co-solubilization compounds identified in the Application, including several of the identified essential oils, gentisic acid and alpha-tocopherol, and proceed in a series of ways identified in the Application and in the context of the art to combine various ratios of those ingredients to create the reversed cubic phase or reversed hexagonal phase material.

D. He or she would use well known techniques for mixing the components, including mixing mg scale amounts by hand in a small (say 20 ml) test tube. This method and amount of material would provide sufficient access the material for all necessary observations, and sufficient material to make such microscopic observation of samples as may be necessary, without being unduly burdensome.

E. Among the routes he or she would take would be: (i) to solubilize the compound in the co-solubilizer(s) and then to mix that combination with the lipid or surfactant and water ingredients (see, Examples 3, 8 and 9 of the patent

application); (ii) to mix all ingredients together at once (see Examples 4, 10 of the patent application); (iii) to mix all ingredients except the essential oil or co-solubilization agent, and then to mix in said essential oil or co-solubilization agent(see Example 11 of the patent application); (iv) to mix all ingredients except the compound, and then to mix in the compound (see Example 1 of the patent application); and (v) to mix all ingredients other than the compound and essential oil or co-solubilization agent, and then to add one and then the other of those (see Example 6 of the patent application). He or she may use heating and cooling in this process as is discussed in Example 1 of the patent application. One of ordinary skill in the art would also know that there are other approaches to mixing the components of lyotropic liquid crystalline systems in the literature which may be used to reach the desired results.

F. He or she would use a phase diagram of this system to guide his or her efforts. As is noted in the declaration of David Anderson dated December 15, 2006 at items 4 and 5, one of ordinary skill in the art would be well versed in the use of phase diagrams. He or she would consult publications to determine if a phase diagram was already prepared and published on the system being prepared. If no such phase diagram is available, one of ordinary skill in the art would know how to prepare a phase diagram. The following is one example of the methodology one of ordinary skill in the art might use to prepare a phase diagram. He or she would prepare approximately 10 to 20 samples, or less, of the selected ingredients at different concentrations. He or she would observe the appearance and viscosity, and then observe and further identify using a polarized optical microscope the phase of the material created, for example, lamellar, cubic phase or hexagonal phase, according to well known techniques mentioned in the Application (at page 23, for example) and in many literature references. Such techniques are practiced by those of skill in the art regularly. He or she would plot those points on a phase diagram according to well known techniques. He or she would limit the work to combinations in which the water / lipid or surfactant ratio was within certain limits, in order to work in the reversed, as opposed to normal, domains. With this preliminary phase diagram information, he or she would estimate which concentrations would be likely to form reversed cubic or reversed hexagonal material, and adjust the concentrations of ingredients accordingly. The Application discusses known general rules for the typical

location or adjacency of the reversed cubic and reversed hexagonal phases relative to one another and to other phases (see for example pages 24-28), and to relative surfactant concentrations generally underlying each phase. The literature contains abundant discussions of general factors affecting location of reversed cubic and reversed hexagonal phases relative to one another and to other phases, and taken together these discussions and guidelines would helpfully guide the work of one of ordinary skill in the art. Put at its most direct, I am confident that any of my research students would be able to take the Application and be able to use the formulation rules it describes and the examples it uses to rapidly determine the correct compositional range in which to solubilize a difficult to solubilize compound in a reversed cubic or hexagonal phase. I would class such an individual as one of ordinary skill in the art.

G. At the completion of this process, he or she would have a composition comprised of the compound and the selected ingredients, and know with certainty whether it was reversed cubic or reversed hexagonal phase material, or another phase.

H. Should he or she wish to do so, they could send a sample of the material off to any of a number of academic or commercial laboratories for standard SAXS (small angle x-ray scattering) analysis, and analyze that data to further confirm, according to well established principles and parameters, the phase of the material, including whether it is reversed cubic or reversed hexagonal phase, and the exact measurements of its structure.

11. The steps noted in item 10 above are the kind of steps one of ordinary skill in the art is accustomed to performing. In my opinion, these steps, depending on resources available, might be performed within a matter of hours by one of ordinary skill in the art after he or she has had an opportunity to review the above-identified patent application. Knowledge of specific percentage ranges of constituents is not required by one of ordinary skill in the art, and it would be known that such percentages would vary depending on the constituents being combined. As noted in David Anderson's declaration dated December 15, 2006, at item 4, one of ordinary skill in the art would be aware that variations in constituents and ratios can lead to significant physical differences in compositions produced and that not every combination of compounds can be combined in a way

that forces the formation of a structured fluid. Rather, one of ordinary skill in the art would have sufficient knowledge and training to easily deduce the constituents and ratios of constituents, based on the teachings in the application, to produce a composition or solvent system which is to include a structured fluid. One of ordinary skill in the art would know that adding a co-solvent/dissolution agent to allow effective incorporation of certain compounds of interest, as is contemplated by the patent application, does not require unfamiliar techniques or undue experimentation. Thus, it is my opinion that one of ordinary skill in the art would be able, upon review of the above-identified patent application, to produce a structured fluid having a reversed cubic phase or reversed hexagonal liquid crystalline phase from any of a number of polar solvents, lipids or surfactants, and essential oils or dissolution/solubilization agents (as are specified in claim 1 of the above-identified patent application for example), and to incorporate any of a number of difficult to solubilize compounds in the structured fluid in an effective amount, and he or she would not need any additional information beyond that which is described in the patent application that he or she would not already know or have access to and would not be required to undertake any undue experimentation to ascertain how to make and use the invention described in the patent application.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Richard Templer, Ph.D.

Date: 7.6.07

Appendix A to Declaration of Richard Templer

Curriculum vitae

Name: RICHARD H. TEMPLER, D.PHIL., FRSC

Education, training, and positions:

1978-81	B.Sc. (first class) Bristol University
1981-86	D.Phil., University of Oxford
1986-88	Lecturer, Princeton University
1988-93	Research Fellow, Southampton University and Imperial College
1993-	Lecturer, Reader and Professor in Biophysical Chemistry, Imperial College London
2002-	Co-Chair of the Chemical Biology Centre, Imperial College
2006-	August von Hofmann Chair in Chemistry, Imperial College
2002-07	Head of Chemistry, Imperial College London
2005-	Chair of AtlantICC an alliance with Oak Ridge National Labs and Georgia Tech
2005-	Non-executive Director of ICON
2006-	Co-founder and Board member of spinout company ChembeCell
2007-	Director of the Porter Institute, Imperial College London

Evidence of Esteem:

Awards:
FRSC (1998)
Royal Society University Research Fellows (1988-93)
Princeton Visiting Fellow (1986-88)
Harkness Fellow (1986-88).

External Committees:
Honorary Chair of the Biophysical Chemistry Group of the RSC (2001-2004)
Chair of AtlantICC, an alliance of Imperial College, Oak Ridge National Laboratory and Georgia Tech (2003-)
Southampton University Chemistry Advisory Board (2003-05)
Member of EPSRC's Technical Opportunities Panel (2004-)
Board of Directors of ICON plc (2004 -)
Doctoral Training Centre Advisory Boards for Warwick (Chair) and White Rose Alliance and for the EPSRC funded Research Consortium "Modelling of the biological interface with materials." (2004-)
Marlow Medal Committee (2005 -)
Faraday Council of the Royal Society of Chemistry (2005-)
RAE sub-panel for Chemistry (2005-)
Standing Committee of Heads of Chemistry UK (2005-)
Chairmanship of 5 EPSRC funding panels (2002-)
Contributor to Royal Society's Biofuels working group (2007)

Editorial work:
Board of "Interface" Royal Society (2004-)

Current major research grants:

GlaxoSmithKline: PI, Studies of Non-Specific Binding of PET Imaging Agents (2003-2007) - £900k

EPSRC: PI (with CBC Board), Doctoral Training Centre in Chemical Biology (2003-2012) - £5M
EPSRC: Co-I, Platform Grant: Self-assembled Amphiphilic Microstructures (2004-08) - £425k
EPSRC: Co-I, Technologies and Techniques for Single Cell Proteomics - £4.8M
BBSRC: Co-I, Quantification, modelling and analysis of molecular dynamics, patterning and signalling in the NK synapse - £750k

Research training provision:
Director, MRes in Biomolecular Science (EPSRC funded), 2000-2003
Director, Doctoral Training Centre in Chemical Biology (EPSRC funded), 2003-
Research Board Member, Alternative Academic Drug Discovery Initiative (GSK funded), 2002-2004
Research Board Member, ABACUS (Merck Pharmaceuticals funded)
Post-doctoral trainees: 10
Post-graduate trainees: 34 Phd students, 3 MSc students, 12 MRes students
Trainees' subsequent positions include: Princeton University, Oxford University, Cambridge University, Imperial College London, Cornell and Reading University

Publications:

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90 Stephen H. Alley, Mauricio Barahona, Oscar Ces and Richard H. Templer "Modelling Lipid Biosynthesis in the Plasma Membrane." Biophys. J. (submitted, 2007)

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